REMARKS

Status of the Claims

Claims 1-100 were pending.

Claims 1-100 were rejected under Section 103.

Claims 1-100 are canceled.

Claims 101-112 are new claims.

Reconsideration is respectfully requested.

I. New Claims

Applicant has cancelled all pending claims and added new claims 101-112. Although this amendment is submitted after final rejection of all claims, applicant requests that the amendment be entered pursuant to 37 CFR § 1.116(b), as it places the claims in better condition for consideration on appeal. Applicant has filed herewith a Notice of Appeal with regard to claims 71, 72, 76 through 79, 90 and 98. The new claims herein correspond substantially in substance to these appealed claims. In particular, new claim 101 herein corresponds substantially in substance with previous claim 71[1], new claim 102 corresponds substantially with previous claim 72, new claims 103-106 with previous claims 76-79, respectively, new claims 107-110 with previous claim 90, and new claims 111-112 correspond substantially with previous claim 98.

It is noted that along with the Notice of Appeal of claims 71, 72, 76 through 79, 90 and 98, applicant has filed a divisional application as to non-appealed subject matter.

II. Response to Office Action Rejections

Applicant gratefully acknowledges that the rejections on grounds of lack of enablement under Section 112, first paragraph, and indefiniteness under Section 112, second paragraph, have been withdrawn. The sole rejection remaining is based on alleged obviousness under 35 USC § 103(a). This argument is addressed below.

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[1] In claim 101, the anti-metabolite may be selected from capecitabine and/or 5-FU. Previous claim 71 was directed to a method wherein the anti-metabolite was capecitabine. As previously discussed, capecitabine enzymatically converts to 5-FU *in vivo*. *See* Amendment filed November 12, 2003, at p. 30.

Each of the claims herein is directed to a method of administering a combination, or a pharmaceutical product involving a combination, of Compound 1 (also now known as "ixabepilone"), and an anti-metabolite selected from capecitabine and/or 5-fluorouracil.

The previously-pending claims, including the method of treating cancer by administration of a synergistic combination of Compound 1 (ixabepilone) and capecitabine, were rejected under 35 USC § 103(a) as being obvious over Vite *et al.*, WO 99/02514, in view of Saeki *et al.*, Mechanism and Possible Biochemical Modulation of Capecitabine (Xeloda), a Newly Generated Oral Fluoropyrimidine (hereinafter "Saeki"). Vite et al., WO 99/02514 corresponds to US Pat. No. 6,605,599, which issued on August 12, 2003, and is assigned to the present assignee. Compound 1 (ixabepilone) is Example 3 of the '599 patent and is specifically claimed in claim 8 therein.

Applicant understands the Office Action's obviousness argument is based on the reasoning that Saeki suggests a combination of capecitabine and other agents, including taxanes, and thus, allegedly it would have been obvious to substitute the "taxanes" of Saeki with Compound 1 of Vite to arrive at the instantly-claimed invention.

Previously, applicant argued that Vite is not properly combined with Saeki, and further, the combination, if appropriate, would not render obvious the instantly claimed invention. Applicant pointed out that Compound 1 herein is much different in structure than for example, the taxane compound paclitaxel, and that Compound 1 is effective in treating paclitaxel-resistant and paclitaxel-sensitive tumors (spec. at p. 21). Thus, applicant argued, there is no basis for an obviousness rejection based on an expectation of similar properties due to similarity in structures, *cf.* MPEP § 2144.09, and no basis to "substitute" the Compound 1 for taxanes in Saeki.

Nonetheless, the Office Action argues a *prima facie* obviousness case is established. In particular, the Office Action argues that it is "*prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose." (Office Action at pp. 3-4, citing *In re Kerkhoven*, 205 USPQ 1069, 1072 (CCPA 1980)). However, this statement in *Kerkhoven* – a case involving a detergent -- does not apply in all fields and in fact, is contradicted by express language in other cases. There are countless

decisions, for example, which emphasize that such a statement cannot be construed as a generally-applicable rule of law, because "virtually every claimed invention is a combination of old elements," and "virtually every patent can be described as a 'combination patent.'" *Medtronic Inc v. Cardiac Pacemakers, Inc.*, 220 USPQ 97, 99-100 (Fed. Cir. 1983). Indeed, this argument in the Office Action is contradicated by another case on which the Office Action relies, *i.e.*, *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In *In re McLaughlin*, the court noted it is well recognized that "[a] patentable invention ... *may* result even if the inventor *has*, in effect, merely combined features, old in the art, for their known purpose, without producing anything beyond the results inherent in their use." *Id.* at 212 (citing *In re Sponnoble*, 405 F.2d 578, 160 USPQ 237 (CCPA 1969) (emphasis in original). Indeed, in *United States v. Adams*, 383 U.S. 39, 51-52 (1966), decided alongside *Graham v. John Deere Co.*, 383 U.S. 1, 17, 86 S. Ct. 684, 693 (1966), the Supreme Court held Adam's patent was *not* obvious, yet the patent there claimed a battery made of materials already known in the prior art for use in making batteries.

This case involves the unpredictable field of chemotherapeutic cancer agents, and as such, the broad statement of *Kerkhoven* is inapplicable. Methods of treating cancer carry with them inherent uncertainties, and one skilled in the field cannot reasonably predict that a combination of two known agents useful individually will be effective for treating the same or different cancer as to which a single agent is effective. Indeed, in this unpredictable field, it is conceivable that two agents individually useful for treating a particular disease could upon combination become disadvantageous for treating the same disease. For example, in Holmes, F., Seminars in Oncology, Vol. 23, No. 5 (October 1996) (hereinafter "Holmes"),[2] in discussing combinations including paclitaxel, the author reports on challenges involved in developing a therapeutic combination:

> "First, an optimal dose and schedule for administration of paclitaxel has not yet been defined .... Second, empiric combinations of standard agents (eg cisplatin and doxorubicin) with paclitaxel have resulted in unexpected and/or severe toxicities related to sequence of administration and schedule. Third, *much of the initial in vitro and preclinical data were not supportive of synergistic combinations*, although more recent data do suggest that combinations *can be additive*. Finally, [hypothesis] ...

[2] The Holmes's article and each of the articles and patent publications discussed herein is being supplied to the USPTO via an IDS submitted concomitantly herewith.

> suggests that a series of high doses of multiple *single* agents may be more effective in treating resistant cells and preventing the development of resistance than simultaneous use of the same agents at lower doses." [*Id.*] [emphasis supplied].

Similarly, in Johnson, K.R. *et al.*, "*5-Fluorouracil Interferes with Paclitaxel Cytotoxicity against Human Solid Tumor Cells*," Clinical Cancer Research, Vol. 3, Issue 10 (1997), at pp. 1739-45, the authors report:

> We found that 5-fluorouracil (5-FU), another antineoplastic agent that usually arrests tumor cells at the G1-S phase of the cell cycle, could significantly repress the cell-killing activity of paclitaxel in solid tumor cells, even when it was added simultaneously with paclitaxel. Further studies indicated that 5-FU actually inhibits the cytotoxic effects of paclitaxel on both mitotic arrest and apoptotic cell death, suggesting that 5-FU might interference with paclitaxel cytotoxicity at an early stage ....Because recent clinical trials have used a combination of paclitaxel and 5-FU in the treatment of metastatic breast cancers, our results also suggest that the combination of these two drugs might not be as valuable in clinical chemotherapy.

See also Johnson *et al., "5-Fluorouracil Interferes with Taxol Cytotoxictyon Human Solid Tumor Cells,"* Proc. Am. Assoc. Cancer Res., Vol. 38, Meet. 88 *(1997) at* p. 323, reporting that "the 2 agents [5-FU and taxol] have a detrimental effect on the each others action ....".

The previous Office Action, in fact, acknowledged that this is an unpredictable field. As such, the comment in *Kerkhoven* cannot be broadly applied as a general rule to reject the instant claims out of hand. Certainly, such broad statements are not a substitute for engaging in a full and proper inquiry into the obviousness question, considering the requirements for determining the alleged obviousness of an invention as expressed by the Supreme Court and the Federal Circuit.

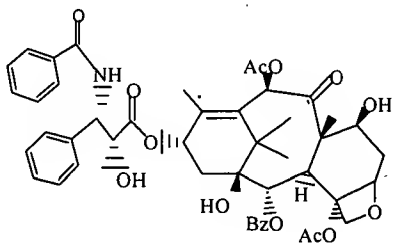
The obviousness inquiry under *Graham v. John Deere Co.*, 383 U.S. 1, 17, 86 S. Ct. 684, 693 (1966), requires that the decision-maker consider: (1) the scope and content of the prior art, (2) the differences between the prior art and the claims at issue, (3) the level of ordinary skill in the field at the time the invention was made, and (4) objective evidence of secondary considerations. *Id.; see also Para-Ordnance Mfg. v. SGS Importers Intern.*, 73 F.3d 1085, 1088, 37 USPQ2d 1237 (Fed. Cir. 1995). Against this backdrop,

obviousness is determined. In considering a conclusion of obviousness, the Federal Circuit has established three essential standards for the USPTO to meet, as a minimum, thus guarding against the application of hindsight and inconsistent decisions. Specifically, a *prima facie* case of obviousness requires findings that: (1) the prior art contains *a suggestion or motivation* for modifying or combining the references; (2) the proposed modifications have a reasonable expectation of success in the prior art; and (3) the references teach or suggest *all* claim limitations. *See In re Chu*, 66 F.3d 292, 36 USPQ2d 1089, 1094 (Fed. Cir. 1995); *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443, 1444-46 (Fed. Cir. 1992); and MPEP § 2143. The burden of satisfying these requirements rests squarely with the PTO. *See Ex Parte Skinner*, 2 USPQ2d 1788, 1789 (Bd. Pat. App. & Inter. 1986); MPEP § 2142.

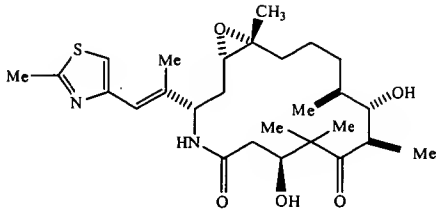
Notably, in *In re Dembiczak*, 50 USPQ2d 1614 (Fed. Cir. 1999), the court emphasized that it will demand a "rigorous application of the requirement for a showing of the teaching or motivation to combine prior art cases." *Id.* at 1617. This is necessary, the court explained, to guard against the "subtle but powerful attraction of a hindsight-based obviousness analysis." *Id.* Thus, under *In re Dembiczak*, for the Examiner to make an obviousness determination based on a combination of references, the Examiner must make "particular findings" based on "actual evidence," and the "showing must be clear and particular." *Id.* at 1617.

Here, no particular findings based on actual evidence have been made. Instead, the Office Action argues that because capecitabine is reported to be effective to treat breast cancer, to have a high efficacy rate and low toxicity, it would have been obvious to make the instantly-claimed combination of capecitabine with Compound 1. This is not evidence or particularized findings, but a conclusory statement that is "entirely inadequate to support the rejection." *Id.* (*quoting In re Sichert*, 566 F.2d 1154, 1164, 196 USPQ 209, 217 (CCPA 1977)). The fact that references can be combined does not render the resultant combination obvious, unless there is a suggestion *in the prior art* for *making* the combination. MPEP § 2143.01. That the taxanes and Compound 1, work generally via microtubule stabilization is not, *ipso facto*, a scientific basis to conclude that these compounds are interchangeable equivalents. Consider again, for example, the vast

differences in structure between paclitaxel, one of the Taxanes, and Compound 1 herein, *i.e.*:



Paclitaxel



Compound 1

Additionally, regarding the scope and content of the prior art and what it appropriately suggests, the combined teachings in a field need to be considered. Just as it is inappropriate to "pick and choose ... elements of assorted prior art references to recreate the claimed invention" (*Smithkline Diagnostic Inc. v. Helena Labs Corp.,* 859 F.2d 878, 887, 8 USPQ2d 1468 (Fed. Cir. 1988)), it is inappropriate for an Examiner to pick from a body of teachings one obscure reference as unequivocally establishing the state of knowledge in the field. Rather, "all teachings in the prior art must be considered to the extent they are in analogous arts," and "[w]here the teachings of two or more prior art references conflict, the Examiner must weigh the power of each reference ...." MPEP § 2143.01. The Office Action argues that a hindsight reconstruction of applicant's invention is proper provided it does *not* take into account knowledge from applicant's disclosure. Office Action at page 3 (citing *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971)). Here, however, knowledge from applicant's disclosure is being applied at each step of the process, *i.e.*, the Office Action has relied upon applicant's disclosure to select Saeki as a reference, to further pick from Saeki a particular group of elements, *i.e.*, capecitabine and taxanes, to combine those selected elements with Vite, to substitute the taxanes with Compound 1 herein, and then to reject the applicant's claims.

Initially, it bears noting that paclitaxel and Compound 1 are not the only known micro-tubule affecting agents and anti-metabolites, respectively. The term "taxanes" itself, which is used in Saeki, includes many species, of which paclitaxel is one example. References establish that micro-tubule affecting agents may include allocolchicine, Halichonrin B, colchicines, colchicinederivatives, dolastatin 10, maytansine, rhizoxin,

paclitaxel, paclitaxel derivatives, Taxotere, thiocolchicine, trityl cysteine, vinblastine sulfate, vincristine sulfate, epothilone A, epothilone, discodermolide estramustine, nocodazole, and MAP 4. (See US 2002/0198216A1, col. 293). The instant Compound 1 (ixabepilone) is an epothilone *analog* and is yet different in structure from epothilones A and B. Other microtubule affecting agents have been identified to include navelbine and teniposide (US 2004/0023925). Likewise, US 2003/0191162 A1 claims combinations of fluorinated pyrimidines with a large number of other chemotherapeutic agents including 5-FU and capecitabine and states that combinations of such compounds with fluorouracil or fluoruracil/leucovorin is expected to be useful for the treatment of colorectal cancer. (col. 41). Besides capecitabine and 5-FU, other specific fluorinated chemoetherapeutic agents are identified including carmofur, doxifluridine, floxuridine, tegafur, and uracil-ftorafur. Further references identify alternate anti-metabolic agents as including Cytosar-U®, DepoCyt™, Fludara®, Sterile FUDR, Leustatin®, methotrexate, purinethol®, and thioguanine® (US Pat. 6,462,017 B1), besides Xeloda® which is capectiabine.

Accordingly, the decision in this case to (a) select capecitabine from the many anti-metabolites, (b) select taxanes from the various micro-tubule affecting agents, (c) select Saeki as the most pertinent primary reference, (d) select taxanes from the other anti-cancer agents recited in Saeki, and (e) then to take the further step of substituting Compound 1 (amongst the various micro-tubule affecting agents), for taxanes, is clearly based on knowledge from applicant's disclosure. It also bears noting the disclosure of Saeki does not even expressly state synergy was found in combinations with capectiabine; instead, Saeki states that "in vivo study showed synergistic *or additive* effects of Capecitabine combined with anti-cancer agents (Taxanes, mitomycin C, or cyclophosphamide), cytokines, growth factors, and hormonal agents."

A proper obviousness analysis would require that the USPTO engage in a first step of determining the scope of prior art reference***s*** in the field and what they teach ***as a whole***, at the time of applicant's invention, including conflicting references. Here, the state of the art at the time of applicant's invention recited many broad combinations of various chemotherapeutic agents. With regard to combinations involving 5-FU and/or capecitabine, for example, WO 01/49287 A1 to Sugen, at pages 41-42, reports that "the precise mode of

action of fluorouracil is not clear," and "[w]hile use of the above combinations [involving 5-FU and various other agents, e.g., methotrexate, leucovorin, interferon, platinum compounds, etc.] is increasing, none of them at present appear to provide a clear advantage over fluorouracil *alone* or fluorouracil in combination with leucovorin." Additionally, the above-cited article to Holmes (pp. 6-7) discusses difficulties encountered with combinations of other agents and paclitaxel and that "much of the initial *in vitro* and preclinical data were not supportive of synergistic combinations." The above-cited articles to Johnson suggest that combinations of 5-FU and paclitaxel may be disadvantageous. An article to Kano *et al.*, "*5-Fluorouracil in Human Carcinoma Cell Lines in Vitro*," British Journal of Cancer, Vol. 74, Issue 5 (Sept. 1996), at pp. 704-10, reports that "simultaneous exposure to paclitaxel and 5-fluorouracil for 24 h showed mainly *sub*additive effects in A549, MCF7, and WiDr cell lines, whereas it showed additive effects in PA1 cells."

Many other publications in the field at the time of applicant's invention, both in the patent and publication literature, discussed various attempts to develop effective combinations of chemotherapeutic agents and the difficulties and uncertainties involved in arriving at an effective combination.

In rejecting the claims herein, the Office Action has not considered the state of the art and has not engaged in a proper obviousness inquiry. Rather, with the benefit of applicant's disclosure, a hindsight selection from the art was performed to "piece together" the invention and reject applicant's claims. For the foregoing reasons, a *prima facie* obviousness case has not been established, and it is respectfully requested that the Section 103(a) rejection be withdrawn.

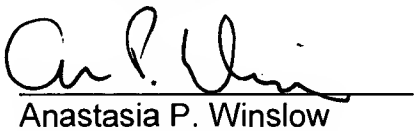
FEES

Applicant has added twelve new claims but canceled 100 claims. Thus, is it believed no fee is due. However, in the event it is determined a fee is due, please charge same to Deposit Account No. 19-3880 in the name of Bristol-Myers Squibb.

SUMMARY

It is believed that all rejections of the claims have been fully addressed and that the instant claims are in condition for allowance. The Examiner is invited to contact the undersigned if it is believed a telephonic communication would expedite the prosecution of this application.

Respectfully submitted,



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